IN THE UNITED STATES PATENT AND TRADEMARK OFFICE
BEFORE THE BOARD OF PATENT APPEALS AND INTERFERENCES

Docket No.: MORENO-LOPEZ

In re PATENT Application of:	)
SONIA MORENO-LOPEZ &	) **Examiner: Anne Marie**
MARCOS TIMÓN-JIMENEZ	) **Sabrina Wehbe**
	)
Appl. No.: 10/816,465	) **Group Art Unit: 1633**
Filed: April 1, 2004	) **Confirmation No.: 8524**
	)
For: MEANS FOR ELICITING AN IMMUNE RESPONSE AND A METHOD THEREFOR	)

BRIEF OF APPEAL

MAIL STOP AF
Commissioner for Patents
P.O. Box 1450
Alexandria, VA 22313-1450

CERTIFICATION OF EFS-WEB TRANSMISSION

I hereby certify that this paper is being EFS-Web transmitted to the U.S. Patent and Trademark Office, Alexandria VA 22313-1450, on **September 3, 2010**
Date

URSULA B. DAY
(Name of Registered Representative)

/Ursula B. Day/ **/09-03-2010/**
(Signature) (Date of Signature)

S I R:

This is an appeal from the final rejection of claims 42-44 by the Primary Examiner. The Brief is being filed under the provisions of 37 C.F.R. §41.37. The amount of $270.00 to cover the requisite fee set forth in 37 C.F.R. §41.20(b)(2) is being paid herewith by credit card.

The Commissioner is hereby authorized to charge fees which may be required, or credit any overpayment to Deposit Account No. 50-1747.

(1) REAL PARTY IN INTEREST

The above-referenced patent application has been assigned to MOLOGEN AG with a place of business at Fabeckstrasse 30, 14195 BERLIN Germany, the real party in interest by virtue of an assignment which was recorded in the Patent and Trademark Office under reel 014879 and frame 0873.

(2) RELATED APPEALS AND INTERFERENCES

There are no and there have been no related appeals of interferences that will directly affect or be directly affected by of have a bearing on the Board's decision in this appeal.

(3) STATUS OF CLAIMS

The following claims are in the proceedings:

Claims 42-44 are not allowed

The following claims are on appeal:

Claims 42-44

Claims 42 and 44 stand rejected under 35 U.S.C. 103(a) as being unpatentable over McCluskie et al. (1999) Mol. Med., Vol. 5, 287-300 (hereinafter: "McCluskie"), in view of U.S. Patent No. 6,451,593 (2002) (hereinafter: "Wittig"), and Makkerh et al., (1996) Current Biology, Vol. 6 (8), 1025-1027 (hereinafter: "Makkerh") .

Claim 43 stands rejected under 35 U.S.C 103(a) as being unpatentable over McCluskie in view of Wittig and Liu et al. (2001), Biomacromolecules, Vol. 2, 362-368 (hereinafter: "Liu").

(4) STATUS OF AMENDMENTS

No amendments after final were filed.

(5) SUMMARY OF CLAIMED SUBJECT MATTER

Claim 42-44 refer to a method of eliciting an immune response in a living being with a vaccine which induces protective immunity to Hepatitis B when administered (specification, page 5 lines 12-16, p. 19 lines 17-21) The vaccine is based on a minimal expression construct that contains only DNA sequences necessary for the expression in eukaryotic cells. The minimal expression construct is a covalently closed, linear, dumbbell-shaped deoxyribonucleic acid molecule (specification, p. 23 lines 20–28; p. 24 lines 1-3) that contains a coding sequence for the hepatitis antigen (p. 22, lines 7-10) under the control of a promoter that is configured to be operable in the living being to be vaccinated and a terminator sequence (specification, p. 16 lines 22-26).

In claim 42 the minimal expression construct is covalently linked to an oligopeptide of a length of 5 to 25 amino acids, at least half of which are a member of the group consisting of lysine and arginine (specification, p. 22 lines 11-16). The vaccine is injected intradermally into the subject to be vaccinated (specification, p.5 lines 12-16).

In claim 43 the minimal expression construct is covalently linked to an oligopeptide which consists of SEQ ID NO. 3 (YGRKKRRQRRR) (specification, p. 22 lines 26-28, p.23 line 1). The vaccine is injected intradermally into the subject to be vaccinated.

In claim 44 the minimal expression construct is covalently linked to an oligopeptide which consists of SEQ ID NO. 4 (PKKKRKV) (specification, p. 22 lines 21-25).

(6) GROUNDS OF REJECTION TO BE REVIEWED ON APPEAL

Issue 1 – whether claim 42 and 44 are patentable under 35 U.S.C.§103(a) over McCluskie in view of Wittig and Makkerh.

Issue 2 – whether claim 43 is patentable under 35 U.S.C.§103(a) over McCluskie in view of Wittig and Liu.

(7) ARGUMENT

Issue 1 – whether claim 42 and 44 are patentable under 35 U.S.C.§103(a) over McCluskie in view of Wittig and Makkerh.

a) MCCLUSKIE TEACHES AWAY FROM THE PRESENT INVENTION

The Invention

The invention resides in the combination of the minimal expression DNA construct attached to the Nuclear Localization Signal (NLS) and used as a vaccine against Hepatitis B injected intradermally. The minimal expression construct contains only sequences that are necessary for the expression of the antigen encoded by the construct.

The Prior Art

The McCluskie reference was made of record in an IDS since the beginning of examination. After applicant filed a declaration swearing back of the earlier cited Schirmbeck reference[1], the Examiner decided to cite the McCluskie reference as the closest prior art.

McCluskie teaches a comparison of immune responses generated by different routes of plasmid administration in mice and non-human primates, plasmid expression vectors in a study focused on routes of administration. Hepatitis surface antigen expressing plasmids were delivered by means of 8 different methods of injections and 6 methods not involving injections. The findings in McCluskie demonstrate that the route of administration of plasmid DNA vaccines influence the strength and nature of the immune response in mice and non-human primates.

Wittig teaches an expressible nucleic acid construct (MIDGE) which contains only sequence information necessary for expressing a gene for RNA and protein synthesis.

[1] Schirmbeck et al: *Priming of immune responses to hepatitis B surfaces antigen with minimal DNA expression constructs modified with a nuclear localization signal pepide*
Springer-Verlag 2001; published online: May 3, 2001; XP-002252260
J Mol Med (2001) 79:343-350; DOI 10.1007/s001090100227

The Makkerh reference refers to an investigation into tolerance of nuclear localization signals (NLS) to mutations. Nothing in the reference shows using the claimed NLS.

MPEP 2143.03(VI) states that "[a] prior art reference must be considered in its entirety, i.e. as a whole, including portions that would lead away from the claimed invention. Accordingly, where cited art teaches away from a claimed feature, the cited art is not available for the purposes of an obviousness rejection." Applicant respectfully submits that McCluskie is teaching away from using minimal expression vectors as claimed in the present invention.

A reference is considered to teach away from the claimed invention when a "person of ordinary skill, upon reading the reference, would be led in a direction divergent from the path that was taken by the applicant."*In re Haruna*, 249 F.3d 1327 (Fed.Cir. 2001) (quoting *Tec Air, Inc v. Denso Mfg.* Mich. Inc. 192 F.3d 1353, 1360 (Fed. Cir. 1999)). The vaccine used in McCluskie is based on plasmid expression vectors. The plasmid vectors in McCluskie contains DNA sequences not necessary for the expression of the antigen in eukaryotic cells. Wittig on the other hand teaches an expression construct which strips away all unnecessary sequences from an expression vector including immunostimulatory CpG motifs. Thus, to arrive at the invention taught in Wittig one would have to remove sequences in the plasmid vectors described in McCluskie that are not necessary for expression including CpG sequences. However, as stated in McCluskie on page 295: "Considerable effort has been expended toward improving the efficacy of DNA vaccines through addition of immunostimulatory CpG motifs to plasmid vectors". And on page 288 of McCluskie: "The induction of strong immune responses in animal models following introduction of DNA appears to be due to ..... the adjuvant effect of unmethylated immunostimulatory CpG motifs present in the DNA backbone". This teaching is in direct opposition to the modifications taught in Wittig. Therefore, a person skilled in the art would indeed be led in a direction divergent from the path taken by the applicant.

This is not changed by the fact that in McCluskie modifications to plasmid vectors other than adding CpG sequences are also mentioned. The question is whether the prior art reference contains teachings that would discourage a

person skilled in the art to modify the reference in a way that would lead to the present invention. The teachings in a reference that encourage modifications that lead to an entirely unrelated invention are not relevant to the question whether there is a teaching that discourages modifications that would lead to the present invention.

The ultimate question is therefore what the combined references would have suggested to a person skilled in the art. While Wittig teaches a vector without classical bacterial plasmid sequences, a person skilled in the art who has both the McCluskie and Wittig references before them would not arrive at a Hepatitis B vaccine based on a pure MIDGE vector. A person skilled in the art who sets out to create an improved DNA vector based vaccine and relies both on McCluskie and Wittig would certainly take the teaching of McCluskie into account. Rather than creating a vector without any classical plasmid sequences at all, a skilled artisan would be motivated to include additional immunostimulatory CpG motifs.

b) COMBINATION OF THE TEACHINGS OF WITTIG AND MAKKERH DOES NOT PROVIDE A BASIS FOR A REASONABLE EXPECTATION OF SUCCESS

The peptide claimed in claim 44 of the instant invention consists of the amino acid sequence PKKKRKV. Neither Wittig nor Makkerh disclose this peptide. Wittig teaches a peptide consisting of 27 amino acid residues which contains the nuclear localization sequence from SV40. In Makkerh, nucleotide sequences coding for various nuclear localization signals were linked in frame to the chicken pyruvate kinase coding region and the resulting fusion proteins tested in cell culture. In the examiner's view Wittig's teaching to link the NLS from SV40 to a dumbbell construct, and Makkerh's teaching of the required core sequence of the SV40 NLS is sufficient for a reasonable expectation of success.

The flaw in the examiner's argument is that she equates characteristics that are necessary with those that are sufficient. In the instant case the examiner

follows the reasoning that since the core sequence of the SV40 NLS has been shown to be necessary it also must be sufficient to provide nuclear localization. This is not correct. There are many instances in science where conditions that are necessary for a certain function are at the same time not sufficient. This is especially the case as here in the field of recognition sequences. For instance, it is well known in the art that restriction enzymes bind to a specific recognition sequence. While this sequence is necessary for the enzyme to target the restriction site, the core restriction site by itself in isolation is not sufficient for the restriction enzyme to function. It is also commonly known in the art that in many cases protein recognition sites are dependent on the particular context in which they appear in order to be functional.

Therefore, it cannot be concluded that because the necessary SV40 core NLS was known, this sequence in isolation must also be sufficient to provide nuclear localization in the instant invention. Moreover, given the knowledge from the analogous field of restriction enzyme recognition sites a skilled artisan would actually have been strongly discouraged to use a minimal core sequence in isolation. Therefore, using the SV40 NLS core sequence in isolation as claimed in the instant invention did not form a basis for a reasonable expectation of success.

Issue 2 – whether claim 43 is patentable under 35 U.S.C.§103(a) over McCluskie in view of Wittig and Liu.

With respect to the combination McCluskie/Wittig the foregoing remarks are applicable in the same manner and are incorporated herein by reference.

With respect to the Liu reference similar considerations apply as in the foregoing discussion. Even the abstract of Liu reveals that the actual peptide sequence that was coupled to the nanoparticles included more than the known necessary core NLS sequence of the HIV TAT protein: "The PTD sequence was constructed upon a solid support, from C-terminus to N-terminus, followed by extension with four glycine residues." (Liu, p. 362). In contrast, the peptide used in claim 43 of the instant invention consists of the amino acids YGRKKRRQRRR

only, without added glycine residues. While Liu showed that the coupled peptide contained the necessary core sequence of the HIV TAT it did not demonstrate that the pure PTD in isolation is also sufficient to confer nuclear localization upon the coupled molecule. Therefore, in analogy to the SV40 NLS discussed above, a person skilled in the art would be discouraged to use the core PTD of HIV TAT in isolation and for that reason there would have been no basis for a reasonable expectation of success.

In conclusion, for the above stated reasons it is respectfully submitted that the rejection of claims 42-43 issued by the examiner on the references should be reversed.

Respectfully submitted,

By:_____/Ursula B. Day/_____
Ursula B. Day
Attorney For Applicant
Reg. No: 47,296

Date: September 3, 2010
708 Third Avenue
Suite 1501
New York, N.Y. 10017
(212) 904-1815
UBD:pn

8) CLAIMS APPENDIX

42. A method of eliciting an immune response in a living being with a vaccine which induces protective immunity to one or more infectious diseases when administered, comprising:

a) providing a therapeutic amount of a product comprising a type 1 cellular mediated immune response eliciting vaccine for injection of the product into a living being to protect against infectious diseases caused by intracellular infection germs; wherein said vaccine comprises:

a DNA expression construct configured to operate in eukaryotic cells;

said expression construct comprising a covalently closed, linear, dumbbell-shaped deoxyribonucleic acid molecule;

said deoxyribonucleic acid molecule comprising a linear double stranded region;

said double stranded region comprising single strands being linked by a short, single- stranded loop consisting of deoxyribonucleic acid nucleotides;

said double-strand forming single strands comprising a terminator sequence; and

a coding sequence for one or more antigens under the control of a promoter that is configured to be operable in the living being to be vaccinated; and

at least one oligopeptide, and

said DNA expression construct being covalently linked to said at least one oligopeptide to increase transfection efficacy, and wherein said DNA construct encodes a hepatitis antigen, wherein the oligopeptide is of a length of five to 25 amino acids and at least half of the amino acids are a member of the group consisting of lysine and arginine, and

b) injecting the therapeutic amount of the product intradermally into the living being.

43. A method of eliciting an immune response in a living being with a vaccine which induces protective immunity to one or more infectious diseases when administered, comprising:

a) providing a therapeutic amount of a product comprising a type 1 cellular mediated immune response eliciting vaccine for injection of the product into a living being to protect against infectious diseases caused by intracellular infection germs; wherein said type-1 cellular-mediated-immune-response-eliciting vaccine comprises:

a DNA expression construct configured to operate in eukaryotic cells;

said expression construct comprising a covalently closed, linear, dumbbell-shaped deoxyribonucleic acid molecule;

said deoxyribonucleic acid molecule comprising a linear double stranded region;

said double stranded region comprising single strands being linked by a short, single- stranded loop consisting of deoxyribonucleic acid nucleotides;

said double-strand forming single strands comprising a terminator sequence; and

a coding sequence for one or more antigens under the control of a promoter that is configured to be operable in the living being to be vaccinated; and

at least one oligopeptide, and

said DNA expression construct being covalently linked to said at least one oligopeptide to increase transfection efficacy, and wherein said DNA construct encodes a hepatitis antigen; said oligopeptide consisting of SEQ ID NO. 3, and

b) injecting the therapeutic amount of the product intradermally into the living being.

44. A method of eliciting an immune response in a living being with a vaccine which induces protective immunity to one or more infectious diseases when administered, comprising:

a) administering a therapeutic amount of a product comprising a type 1 cellular mediated immune response eliciting vaccine by injecting theproduct into a living being to protect against infectious diseases caused by intracellular infection germs; wherein said type-1 cellular-immune-response-eliciting vaccine comprises:

a DNA expression construct configured to operate in eukaryotic cells;

said expression construct comprising a covalently closed, linear, dumbbell-shaped deoxyribonucleic acid molecule;

said deoxyribonucleic acid molecule comprising a linear double stranded region;

said double stranded region comprising single strands being linked by a short, single- stranded loop consisting of deoxyribonucleic acid nucleotides;

said double-strand forming single strands comprising a terminator sequence; and

a coding sequence for one or more antigens under the control of a promoter that is configured to be operable in the living being to be vaccinated; and

at least one oligopeptide consisting of SEQ ID No. 4, wherein

said DNA expression construct is covalently linked to said at least one oligopeptide to increase transfection efficacy, and wherein said DNA construct encodes a hepatitis antigen.

(9) EVIDENCE APPENDIX

NONE

(10) RELATED PROCEEDINGS APPENDIX

NONE